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EXAMINER

KISHORE, GOLLAMUDI S

ART UNIT	PAPER NUMBER
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1615

DATE MAILED: 05/20/2003

18

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/555,986

Applicant

Cevc

Examiner

Gollamudi Kishore

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Feb 13, 2003
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 58-193 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 58-193 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other:

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DETAILED ACTION

The request for the continued examination and the preliminary amendment both dated 2-13-03 are acknowledged.

Claims included in the prosecution are 58-193.

Claim Rejections - 35 USC § 112

- 1. The following is a quotation of the first paragraph of 35 U.S.C. 112:**

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

- 2. Claims 58-193 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific combination of substances (first substance, second substance and third substance), specific liquid medium, does not reasonably provide enablement for claims as claimed with confusing terminology. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Claims are recited in a very vague and confusing way and the specification does not provide adequate guidance as to the nature of the claimed composition.**

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Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that as set forth in the application, amphipathic molecules, namely the macro molecules or chain molecules associate better with an extended surface which comprises at least one amphipathic substance, which tends to form extended surfaces (the first substance) and at least one more substance, which is more soluble in suspending liquid medium and also which tends to form less extended surfaces (the second substance) than the former amphipathic substance. This argument is not found to be persuasive. First of all, the three substances are not clearly defined and differentiated in the specification. There is a considerable overlap between the classes and it is unclear how one class forms more extended surface than the other (there is no very specific definition of extended surfaces either; it is well known in the art that the amphipathic substances form a bilayer structures). The first and second class substances include phospholipids and it is unclear how the phospholipids are more soluble and less soluble in an aqueous suspending medium. It is unclear as to how surfactants such as Tritons (second substance) can form an extended surface by themselves when they are water soluble and form solutions. With regard to chain molecules (third substance), one of ordinary skill in the art would not be able to determine which of the compounds come under this category since even sterols which do not have chain moieties are recited in the specification as belonging to this class. Furthermore, according the claims and the specification, the second and the third substance can be the same. If so, it is unclear as to how one can form the extended surface

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and the other does not, but attaches itself on the second substance. The specification also does not provide a clear definition of 'edge acting substance' and how it is distinguished from surfactant. In fact, the examiner points out that even phospholipids are considered as surfactants. Finally, it should be pointed out that the specification describes one methodology and it is unclear as to how by this method alone one can form different extended surfaces. In essence, The specification is very confusing and not enabling for one of ordinary skill in the art to practice the invention without undue experimentation (see also the discussion below).

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 58-193 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant cancels the originally presented claims and presents new claims with the same issues which existed before and without addressing the issues. For example, as already indicated, if a substance is soluble in a liquid (regardless of the degree of solubility) how can it form an extended surface? What is meant by an extended surface? If all three are amphipathic substances, why would only two form extended surfaces and the third one

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not? What is the solubility of the third amphipathic substance? The examiner had already suggested naming these substances and the third substances. 'less extended', 'more extended' are indefinite since they are relative terms.

Applicant's lengthy arguments have been fully considered, but are not found to be persuasive. Applicant argues that the term, 'extended surface' is known in the art, but provide no evidence to the effect. Applicant's arguments with regard to the issue of solubilities raised by the examiner are also not persuasive for the following reasons. First of all, there is no clear cut definition of the three substances in the specification. The often used word to describe each of the classes is 'type' and there is a considerable overlap between the compounds in the three classes (surface active polypeptide which is a chain molecule is in fact recited as a surfactant belonging to the class second amphipathic substance in claim 101). According to claim 58, the extended surface formed by the first substance is greater than that formed by the second substance. A careful examination of the specification indicates (see page 18 of the specification) the inclusion of compounds such as sterols in the first class of compounds and sterols by themselves do not form vesicles or extended surfaces. They are generally used in liposomal art in combination with a bilayer forming amphiphilic compound such as a phospholipid. Secondly, the term, 'extended surface' as applied to two compounds, in the absence of specific definition can be interpreted in two ways. One :- molecules of each class in side by side existence thus forming an extended surface; 2) class 2 compound binding to the end of class 1 compound

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and thus, extending the surface vertically (see the limitation “wherein the extended surfaces formed by the first substance are greater than the extended surfaces formed by the second substance” in claim 58). With regard to the solubility issue raised by the examiner:- once again a careful examination of the compounds in each class listed in the specification indicates that several of them are lipophilic (phospholipids recited in each class for example) and therefore, are not soluble at all in an aqueous medium (while surfactants such as Tritons are water soluble). Therefore, the limitation in claim 58 “solubility of the second amphiphilic substance in the liquid medium is greater than the solubility of the first amphipathic substance” is very confusing and does not clearly point out and distinctly claim the subject matter. Therefore, the examiner previously suggested defining each class in terms of specific compounds in the claims and restructure the claims to clearly indicate what is being claimed.

The examiner suggests claiming the composition in terms of specific components and name the liquid medium.

Applicant's arguments with regard to the terms, “less” are not found to be persuasive. This term is used in claim 105 for example in combination with the expression, “less capable of forming the extended surface”. What does this expression mean? Either a substance forms an extended surface or does not form an extended surface; how can it be in between?

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The amended claim 58 now recites 'chain molecule'. According to the definition on page 10 of the specification, a chain molecule is any straight or branched chain molecule. Adrenocorticoids and androgens recited in claim 128 are not chain molecules at all. The difference between the 'edge active substance' and 'surfactant' is unclear. According to page 10 of the specification, both appear to be the same. Furthermore, claim 128 recite improper combination of Markush members. Some are specific compounds and the others are generic terms (psoriasis drug, sleep inducing agent for example). Antibiotics recited are wound healing agents which is also recited as a Markush member. Similar is the case with claim 101. For example, this claim recites monovalent salts of cholate and deoxycholate as well as the individual salts such as sodium deoxycholate. This claim recites 'fatty acid salts' as the Markush member and then recites also the individual fatty acid salts. These are just examples. Claim 101 also recites the term 'corresponding' at several places; it is unclear as to which Markush members this term is applicable. It is unclear as to what is being conveyed by 'surface active polypeptides'. Proteins and polypeptides in general have surface active properties.

According to claim 99 which is dependent from 58, the second and the third substance are identical; if so which forms the extended surface and which substance attaches to the second substance?

What is meant by 'adrenolite' as recited in claim 162? (similar terms are also recited in claim 126; rhinologicum for example).

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‘miniature droplets’ in claim 172 lacks an antecedent basis in claim 58.

Furthermore, it is unclear where the third substance is attached as recited in this claim.

According to the parent claim, the third substance is on the second substance; according to claim 172, the third substance is on the droplet surface. This is confusing.

According to claim 58, even the third substance is amphipathic; this means it is totally amphipathic and thus, claim 191 which recites the third substance as ‘partially amphipathic’ is inconsistent with the parent claim.

5. Claims 186-193 provide for the use of the combination, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 186-193 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

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The examiner had already suggested a careful revision of all the claims and reciting them according to US practice so that a proper search can be made. The examiner once again requests a thorough revision of the claims, especially in view of lengthy and numerous claims.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 58-193 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 92/03122 of record.

WO discloses a composition containing two or more amphiphilic substances with different solubilities for the administration of various active substances including insulin (note the abstract and entire publication, in particular, examples and claims).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant once again argues that WO 92 does not disclose the combination of the first, second and the third substances. In particular, applicant argues that WO does not describe or suggest the association of macro molecules to the extended surface. This argument is not persuasive since the reference appears to teach the same combination of amphiphathic substances together with the active agents such as insulin(see Examples 163-

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165-175 in the reference). A careful review of instant specification indicates the use of insulin. Since the method of preparation appears to be the same, the association of the macromolecule to the extended surface is inherent. This rejection will be reconsidered upon the review of an English translation or English equivalent. Applicant's help in this regard is requested (same inventor in both cases).

8. Claims 58-61, 63, 66-76, 91-96, 98, 101, 117, 126-127, 157-171, 174, 186, 187, 189-192 are rejected under 35 U.S.C. 102(b) as being anticipated by Uster (4,944,948).

Uster discloses a combination of three amphipathic substances and formation of vesicles. The combination includes two phospholipids, PC, PG and a macromolecule, EGF. The compositions further contain cholesterol (note the abstract, col. 4, lines 1-32 and col. 8, line 29 et seq.).

9. Claims 58-60, 63, 66-74, 91-98, 100-101, 110-122, 151-152, 171-180, 186, 189-192 are rejected under 35 U.S.C. 102(b) as being anticipated by Klivanov (BBA , 1991).

Klivanov discloses liposomes containing three amphipathic substances. They include phospholipids and cholesterol. The third amphipathic substance which is on the surface is either PEG or an antibody (note the summary and page 143). The reference meets the requirements instant claims.

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Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. Claims 58-193 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/03122 cited above, in further combination with either Uster (4,944,948) or Klibanov cited above.

The teachings of WO have been discussed above. In essence, WO basically teaches a combination of the three amphipathic substances claimed. What is unclear from WO is whether the third substance (macromolecule) is on the surface of the vesicles. Assuming that it is not, attaching a macromolecule on the surface, if that is desired, is deemed obvious to one of ordinary skill in the art since the reference of Uster teaches that when a macromolecule such as EGF can either be encapsulated or attached to the surface of the vesicles with the same release rates (abstract and col. 8, line 29 et seq., col. 10, line 61 et seq.). One of ordinary skill in the art would expect at least similar results. Uster further teaches on col. 4, lines 26-32 that the negative charge on the vesicles enables the EGF

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molecules to adsorb on the surface of the vesicles. Although Uster does not teach macro molecules other than EGF, WO teaches a variety of macro molecules and it would have been obvious to one of ordinary skill in the art based on Uster's statement that any macromolecule could be attached to the surface of the vesicles, if such is desired and with the expectation of obtaining at least similar results. One of ordinary skill in the art would be motivated to use an amphipathic molecule such as PEG since Klibanov teaches that such a use would increase the circulation time of the vesicles.

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12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *G.S. Kishore* whose telephone number is (703) 308-2440.

The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T.K. Page, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-3592.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [thurman.page@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

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Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-1235.



Gollamudi S. Kishore, Ph. D

Primary Examiner

Group 1600

gsk

May 19, 2003